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Review Article

The interplay between Sars-Cov-2 infection related cardiovascular diseases and depression. Common mechanisms, shared symptoms

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ABSTRACT

In 2020 the World Health organization announced a pandemic due to the outbreak of the Coronavirus disease 19. Pneumonia was the most common manifestation of the Sars-Cov-2 infection, however, clinical papers describe Sars-Cov-2 associated cardiovascular pathologies, such as ACS, myopericarditis, cardiomyopathies, dysrhythmias, as leading causes of increased morbidity and mortality. The short and long term prognosis of Sars-Cov-2-related cardiovascular diseases was defined not only by the disease severity itself but also by associated conditions and complications, among which mental health issues (stress, depression and anxiety) have a negative impact. The interplay between Sars-Cov-2 infection, cardiovascular disease and depression may be explained by hyperinflammation, unhealthy lifestyle and inter-organ communication, mediated by extracellular vesicles (EV) and non-coding MicroRNA (miRNA). The long Covid syndrome is characterized with orthostatic hypotension, impaired cardiac and cerebral perfusion, postural orthostatic tachycardia syndrome (POTS), syncope, chest pain, dyspnea, palpitation, chronic fatigue syndrome, 'brain fog', memory, cognitive and sleep difficulties, depression and anxiety. From a clinical point of view these symptoms may be considered as common symptoms representing not only a cardiac but also a neurological/psychiatric problem. Consequently assessment of these symptoms are of paramount importance. Due to their complexity, management of these patients requires multidisciplinary care.

In 2020 the World Health Organization announced a pandemic due to the outbreak of the Coronavirus disease 19 (Sars-Cov-2) [1,2], Pneumonia was the most common manifestation of the Sars-Cov-2 infection, however, clinical data from multiple reports suggest cardiovascular manifestations, thromboembolism and multiorgan failure as Sars-Cov-2 infection related complications [3–5].

1. Mechanisms

Three following mechanisms were suggested as mediators of Sars-Cov-2-related inflammation:

1. Direct invasion - the virus binds to ACE 2 receptors and is then cleaved by type 2 transmembrane serine protease (TMPRSS2), which facilitates the fusion of viral and cellular membranes [6].
2. An Indirect injury - viral replication induces the downregulation of ACE 2 receptors and activation of Angiotensin II type 1 receptors (Ang II/AT1) leading to vasoconstrictive, proinflammatory, prooxidant, and procoagulant effects [7].
3. Systemic inflammatory response - activation of T and B lymphocytes (B/T cells) and inflammatory cytokines (interleukines, tumor necrosis factor-a (TNF-a)) promotes oxidative stress and production of free radicals resulting in endothelial dysfunction [7,8].

Abbreviations: EV, extracellular vesicles; ACE2, angiotensin-converting enzyme 2; miRNA, microRNA; POTS, postural orthostatic tachycardia syndrome; Sars-cov-2, coronavirus disease 19; STEMI, ST-segment elevation myocardial infarction; hs-cTnT, high-sensitive cardiac troponin T; CRP, C-reactive protein; ACS, acute coronary syndrome; NACR, National Adult of Cardiac Rehabilitation; BBB, brain-blood-barrier; BCSFB, blood-cerebrospinal fluid barrier; Ang II/AT1, angiotensin AT1/AT2 receptors; TLRs, Toll-like receptors; TNF -a, tumor necrosis factor-a; B/T cells, T and B lymphocytes; KYN/TRP, kynurenine/tryptophan; TMPRSS2, transmembrane serine protease 2; RAAs, renin-angiotensin-aldosterone system; PTSD, post-traumatic stress disorder; SH, systemic immune inflammation index; Cardiac MRI, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; LF, low frequency.

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2. Sars-Cov-2 and cardiovascular inflammation

Immune-mediated cytokine storm promotes activation of platelets, toll-like receptors (TLRs), and macrophages leading to platelet aggregation, hypercoagulation, micro and macroangiopathy, and consequent vascular thrombosis [7,9]. Macrophage-induced disruption of atherosclerotic plaques results in type 1 myocardial infarction [7,10,11]. Hyperinflammation also may induce a mismatch in myocardial supply-demand and type 2 myocardial infarction [7].

Data from the largest cohort study (36 309 patients) show that 565 patients with out-of-hospital ST-segment elevation myocardial infarction (STEMI) and 359 patients with in-hospital STEMI had a concomitant Sars-Cov-2 infection [12]. Studies report that there was no evidence of obstructive coronary lesions in most patients (around 40%) with STEMI and Sars-Cov-2 infection [13,14]. An observational study of 115 patients demonstrated an increased thrombotic burden and poor prognosis in patients with confirmed STEMI and concomitant Sars-Cov-2 [15].

Apart from myocardial infarction cardiomyocyte damage may be clinically manifested as myocarditis, cardiomyopathy, and even cardiogenic shock [16]. Cytokine-induced myocardial cell injury contributes to the activation of heat-shock proteins, leading to further inflammation, mechanical and arrhythmic complications, and cardiomyopathy [16]. Symptoms related to mechanical and arrhythmic complications include chest pain, dyspnea, and palpitation [10]. A multicenter study across six acute hospitals used cardiac magnetic resonance imaging (MRI) for the assessment of Sars-Cov-2 related myocardial injury [17]. Non-ischemic type of late gadolinium enhancement (LGE) was demonstrated in 26 % of patients, ischemic type LGE was seen in 22 % of patients, and dual pathology was seen in 6 % of patients [17]. It should be emphasized that 66 % of patients did not have a known history of ischemic heart disease or pre-existing heart disease [17,18]. According to the German cohort study of 100 Sars-Cov-2 patients myocardial inflammation was the most prevalent (60 % of cases) abnormality, detected by cardiac MRI [19]. Other abnormalities included late gadolinium enhancement (LGE) typical for myocardial ischemia and pericardial enhancement [19].

Clinical papers report increased morbidity and mortality in patients with Sars-Cov-2 infection and concomitant cardiovascular pathologies, such as acute coronary syndrome (ACS), myopericarditis, cardiomyopathies (including takotsubo cardiomyopathy) and cardiac dysrhythmias [20] [21]. According to a Chinese study predictors of adverse clinical outcomes were severe cardiac injury (OR 2.4, 95%CI 1.8–20.1), hypotension during treatment (OR 3.4, 95%CI 2.1–17.1), and pericardial effusion (OR = 3.5, 95%CI 1.8–15.1) [22]. The short-term mortality was 20 % and major adverse events occurred in 35 % of patients with Sars-Cov-2 and myocardial injury [23]. Both cardiac MRI and high-sensitive cardiac troponin T (hs-cTnT) above sex-specific 99th percentile URLs were considered as independent predictors of prognosis in patients with Sars-Cov-2 infection [23,24]. A mortality of 22 % was seen in patients with cTn above URL, versus 61.5 % of those with cTn levels >10 times the URL [25]. Findings from a multicenter cohort study of patients with Sars-Cov-2 infection suggest that hs-cTnT <6 ng/l was related to better outcomes, with a negative predictive value of 94.9 % (87.5–98.6 95 % CI), [23]. However, according to the COVID-HEART prospective, longitudinal, multicenter, observational cohort study only late gadolinium enhancement (LGE) but not troponin was an independent predictor of major adverse cardiac events (MACE) - odds ratio, 2.25 (1.12–4.57 95% CI) [24].

The short and long-term prognosis of Covid-19-related cardiovascular diseases was defined not only by the disease severity itself but also by associated conditions such as stress, depression, and anxiety [26]. 20 % of patients with acute coronary disease have major depression, and depressive symptoms are even more frequent [27]. According to the National Adult of Cardiac Rehabilitation (NACR) registry, patients with coronary artery bypass grafting (CABG) and heart failure had an increased risk of newly developed depressive symptoms (odds ratio 1.47 (1.25–1.73 95%CI) and 1.33 (1.19–1.48 95%CI) respectively) [28]. See Table 1.

3. Sars-Cov-2 neuroinvasion and neuroinflammation and brain-heart cross-talk

Neuroinvasion of the virus occurs either via hematogenous or neuronal routes [6].

The virus binds to ACE2 in vascular endothelium or infects leukocytes (macrophages) that cross the blood-cerebrospinal fluid barrier (BCSFB) or brain-blood barrier (BBB), known as the Trojan horse mechanism [6,29,30].

Neuronal invasion of the virus occurs via olfactory, trigeminal, and vagus nerves through the, nasal cavity, rhinopharynx and lower respiratory tract [6].

Viral-induced cytokine storm increases the permeability of BBB [31,32], leading to inflammation in neuronal tissue and activation of microglia and astrocytes and subsequent neurodegenerative and neuropsychiatric diseases (stroke, mental health-related, conditions such as depression, anxiety, insomnia, dementia etc.) [31,32]. Activated cytokines inhibit hippocampal glucocorticoid receptors and contribute to the generation of reactive oxygen species [31,33]. High levels of pro-inflammatory cytokines (IL-6 and C-reactive protein) and glial activation enhance the conversion of tryptophan into kynurenine and hyper-activation of the kynurenine pathway and it's toxic metabolites (quinolinic acid, 30-hydroxykynurenine, and 3-hydroxy-anthranilic acid) leading to decrease serotonin synthesis and therefore depressive disorder [34,35]. In addition, the virus can reach brain micro vessels leading to endothelial dysfunction and microthrombotic events [36].

Some studies found higher levels of C-reactive protein (CRP) in Sars-Cov 2 patients with self-reported depression [37]. A Chinese cross-sectional study of Sars-Cov 2 patients showed a positive correlation between depression severity and CRP, while the decreased level of CRP from the baseline was related to a decreased depressive score [38].

Table 1
Depressive symptoms in patients with Sars-Cov-2 infection and long Covid syndrome.

Paper	Study sample	Results
Serdar Sever [28]	The National Audit of Cardiac Rehabilitation (NACR) registry	Receiving CABG or other treatments were associated with an increase in the odds of having new-onset depressive symptoms at the start of cardiac rehabilitation with 47 % and 24 % respectively (OR: 1.47, 95%CI: 1.25, 1.73; OR: 1.24, 95%CI: 1.08, 1.43). Patients who had heart failure were 33 % more likely to have new onset depressive symptoms (OR: 1.33, 95%CI: 1.19, 1.48).
Bai [70]	A single-center prospective cohort study was conducted at San Paolo Hospital in Milan, Italy. Study population: adult patients who were evaluated at the post-COVID outpatient service. Participants were individuals who had clinically recovered from COVID-19 and in whom virological clearance had occurred. A total of 377 patients were enrolled in the study.	A diagnosis of long COVID syndrome was made in 260/377 (69 %) patients. The most common reported symptoms were fatigue (149/377, 39.5 %), exertional dyspnoea (109/377, 28.9 %), musculoskeletal pain (80/377, 21.2 %), and “brain fog” (76/377, 20.2 %). Anxiety symptoms were ascertained in 71/377 (18.8 %) individuals, whereas 40/377 (10.6 %) patients presented symptoms of depression. Post-traumatic stress disorder (defined by a pathological IES-R score) was diagnosed in one-third of patients (85/275, 31 %).

A case-control observational study findings demonstrated that decreased tryptophan and increased kynurenine levels were correlated with increased levels of Il-6 and therefore with disease severity in patients with Sars-Cov-2 [34]. Results from an Italian cohort study indicate that Sars-Cov-2 positive patients with lymphopenia had an increased kynurenine/tryptophan ratio that reflects an increased inflammatory burden [39]. Findings from the UPBEAT UK study indicate that CRP levels, IL-6 expression, and kynurenine/tryptophan (KYN/TRP) ratio were significantly higher in depressed patients with coronary heart disease compared with non-depressed ones [40].

Overactivation of the kynurenine pathway is associated with a high risk of acute myocardial infarction in patients with stable angina [41]. In mice models, acute myocarditis was linked with decreased tryptophan and increased kynurenine levels [42].

Taken together, these findings indicate that the activation of kynurenine pathway in Sars-Cov-2 could be responsible for both cardiovascular and psychiatric (depression) complications and may play an important role in brain-heart crosstalk [34,40,73] (Fig. 1).

Along with systemic inflammation, brain-heart crosstalk is based on extracellular vesicles (EV), which carry biological information and can mediate inter-organ communication between the heart and brain in patients with Sars-Cov-2 infection [43]. These extracellular vesicles are secreted by cells, containing miRNAs and mRNA proteins [43]. Brain-derived extracellular vesicles may promote the release of inflammatory proteins, leading to systemic inflammation and involvement of the cardiovascular system [43]. In patients with Sars-Cov-2 infection, high levels of EV were related to increased coagulation and thrombotic events [44]. Owing to their mediating role in interorgan communication, non-coding miRNAs could be used as biomarkers of Sars-Cov-2-related inflammation as well as for prognostic purposes [44].

Apart from systemic inflammation, social context should be considered as an important contributor to depressive symptoms. The covid-19 pandemic was related to isolation, financial issues, stress, and depressive mood, which itself led to unhealthy behaviors, such as increased smoking, limited physical activity, consumption of cholesterol-rich food, carbohydrates, and weight gain, which are well-known traditional risk factors for cardiovascular diseases [6,8]. Increased levels of stress and anxiety could trigger cardiac arrhythmias, acute myocardial infarction and takotsubo cardiomyopathy [36]. During the Covid-19 pandemic patients with cardiovascular diseases experienced even more worsening of their mental health status (mainly due to restrictions and isolation), affecting the quality of their life [8]. HeartSleep study findings indicate that insomnia, anxiety, and depression have a negative impact on the coping process in patients with heart failure, especially during a stressful time such as a COVID-19 pandemic [45].

In summary, the interplay between Sars-Cov-2 infection, cardiovascular diseases, and depression can be attributed to multiple mechanisms, involving hyperinflammation, non-coding miRNA, unhealthy lifestyle and social restrictions [16].

4. Gender difference in Sars-Cov-2 related inflammation

Studies report sex-related differences in ACE 2 expression. In particular, western analyses of human airway smooth muscle cell lysates demonstrated lower expression of ACE 2 in females vs males, which was explained by possible protective effects of estrogens [46]. Males are more susceptible to the Sars-Cov-2 infection due to the following factors contributing to virus entry: androgen-induced expression of transmembrane serine protease 2 (TMPRSS2) [47] and testosterone-related overexpression of ACE 2 receptors [46,48].

The evidence from multiple studies highlighted that sex hormones influence different innate and adaptive immune responses [49,50]. Testosterone is recognized as immunosuppressive, while estrogens are promoting the immune response [50]. Due to the anti-inflammatory properties of estrogens, women have a more benign time course of the infection and a better prognosis compared to men [47]. The same trend was observed in animal studies - mice males were more susceptible to Sars-Cov infection and were characterized by higher inflammatory response and more severe lung injury [51].

Along with sex hormones, increased immune response and consequent adverse outcomes in men could be attributed to increased levels of proinflammatory cytokines, ferritin, and CRP, especially in elderly age

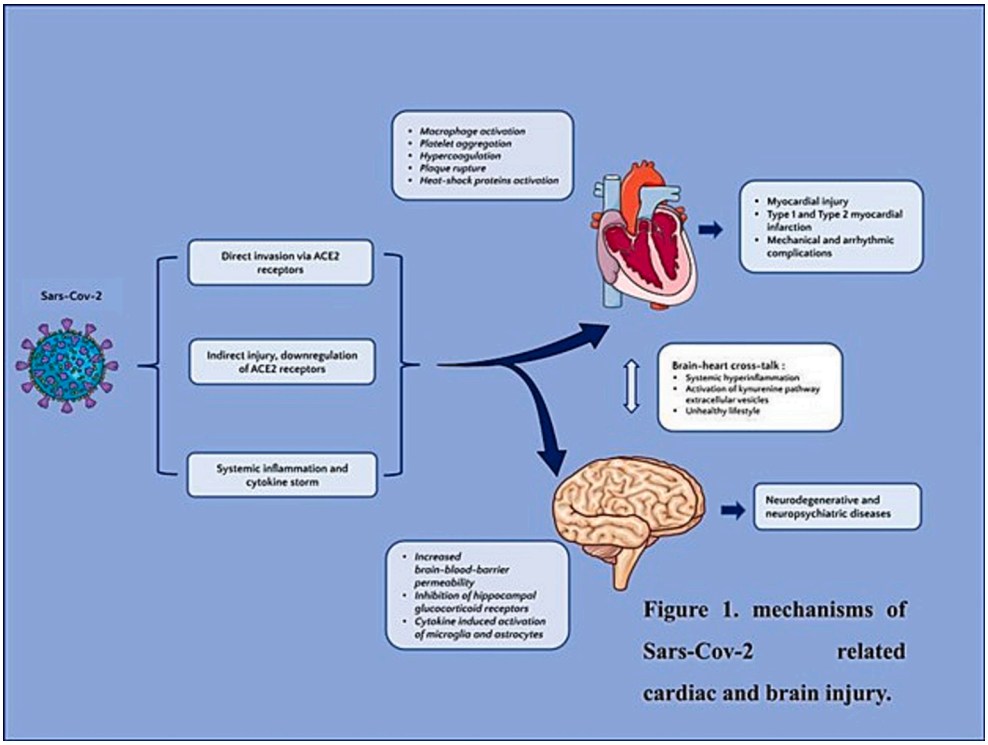

Fig. 1. Mechanisms of Sars-cov-2 related cardiac and brain injury.

[52,53].

However, the protective effect of the female sex is mitigated by the presence of classic cardiovascular risk factors, and coronary calcifications in women as demonstrated by the sCORE COVID-19 (calcium score for COVID-19 Risk Evaluation) study [54].

A particular attention should be paid to Sars-Cov-2 related takotsubo syndrome, which was more common in Sars-Cov-2 positive elderly females compared to males [55]. Age-related estrogen deprivation, increased cortisol and catecholamine release, and renin-angiotensin-aldosterone system (RAAs) system dysfunction may facilitate a high strain to cardiac muscle, leading to takotsubo syndrome [36].

5. Long Covid syndrome, neuro-cardiologic complications and prognosis

The long Covid syndrome (post-Covid syndrome) is defined as: "the condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of Sars-Cov-2, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" [56]. Long Covid syndrome is a complex condition that involves multiple organ systems [57]. It has two phases: post-acute (from 3 weeks to 3 months from the onset of symptoms) and chronic (>3 months) [58].

A long Covid syndrome may be clinically manifested with orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), syncope, chest pain, dyspnea, palpitation, chronic fatigue syndrome, 'brain fog', memory, cognitive and sleep difficulties, anosmia, headache, signs of impaired cardiac and cerebral perfusion, depression and anxiety [57,59,60]. A higher prevalence of psychiatric syndromes - post-traumatic stress disorder (PTSD) (28 %), depression (31 %), anxiety (42 %), insomnia (40 %), and obsessive-compulsive (OS) symptoms (20 %) was also reported [61]. Long-Covid has a negative impact on patient's quality of life. A German cross-sectional study of 1027 patients demonstrated that 49 % of patients with post-covid syndrome reported activity limitations and participation restrictions [62].

Main mechanisms of long-Covid syndrome involve autonomic dysfunction (imbalance of parasympathetic and sympathetic systems) due to cytokine-induced hyperinflammation, oxidative stress, and mitochondrial damage [57,59]. The imbalance of parasympathetic and sympathetic systems leads to impaired function of cardiovascular and neurological systems [59]. A small cross-sectional study of long Covid patients demonstrated that patients had a higher mean heart rate and higher low frequency (LF) indices, indicating vagal dysfunction, dysautonomia, and increased pro-inflammatory state [63]. Similar findings were seen in a prospective study of 103 patients who had disturbed diurnal heart rate variability, and an impaired sympathovagal balance 252 days after infection [64].

Prolonged autoimmune neuroinflammation and persistent viral load in the central nervous system can contribute to late psychiatric syndromes, such as depression, anxiety, and PTSD [29]. Sars-Cov-2-related, prolonged immune response affects brain vessels leading to destruction of BBB, brain cell infiltration and astroglial inflammation, which can result in depression, anxiety, and insomnia [65].

According to an Italian study, the baseline systemic immune inflammation index (SH) was positively associated with anxiety and depression [61]. However, severity of anxiety, insomnia, and PTSD decreased within a 3 months period [66]. More stronger correlation was observed between depression and SH in the follow-up period [66]. Depression symptoms severity was decreased in patients, who showed a marked decrease of SH at 3 months follow-up period, while in those with minor changes in SH depressive symptoms persisted or even worsened [66]. Severe depressive symptoms also predicted poor performance in information processing in the follow-up period [66]. Findings from a Chinese cross-sectional study suggest that the 10-year coronary heart disease risk was higher in post-covid 19 patients with major depressive disorder and higher SH index [67].

An Italian prospective cohort study of Sars-Cov-2 patients showed that depression and PTSD were related to severe inflammation and decreased gray matter volumes in the anterior cingulate gyrus or insular cortex [68]. Authors suggest that gray matter and white matter microstructure and function may mediate a relationship between systemic illness (Sars-Cov-2) and psychiatric outcomes [68].

Along with biological mechanisms, other factors such as social isolation, confinement, as well as acute infection-related trauma, and persistive fatigue could be considered as possible contributors to neuropsychiatric manifestations of long-Covid syndrome [69].

Evidence from clinical studies demonstrated that the risk of long-Covid syndrome is 3 times higher in women and characterized by both physical and psychological burdens [70]. Women with long Covid syndrome reported persistive and residual symptoms of fatigue, dyspnea, increased levels of breathlessness, musculoskeletal pain, and disabilities (visual, memory, walking) compared to males [70,71]. The high prevalence of long Covid syndrome in female patients was explained by a high level of IgG antibodies [72].

From a clinical point of view symptoms of dyspnea, palpitation, and chest pain can be considered as shared symptoms representing not only a cardiac but also a neurological/psychiatric problem. Consequently, assessment of these symptoms is of paramount importance, and due to their complexity, management of these patients requires multidisciplinary care.

In summary, Sars-Cov-2-related cardiovascular and neuropsychiatric manifestations are based on complex mechanisms that can share common pathways and symptoms and therefore their management requires the use of an integrated approach.

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Declaration of competing interest

We have no conflicts of interest to disclose.

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